Summary of the Office Action

Claims 5-8 are pending and are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 5-8 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner has maintained the enablement rejections on the basis of the previously cited references (see the Office Actions dated July 17, 2000 and April 11, 2001). First, the Examiner argues that Grisanti et al. teach that RPE cells elicit immune responses when transplanted. The Examiner further argues that Enzmann et al. teach that immune responses occur in the posterior part of the eye and that Craaford et al. teach that cells transplanted into the eye are rejected by the recipient. In the case of Craaford, the Examiner argues that there is no long term survival of the transplanted cells, and photoreceptor degeneration occurs in areas adjacent to the sites of rejection. Finally, the Examiner cites Valtink et al. as teaching that immunological failure must be prevented for successful methods to be developed and, furthermore, that there is a possibility of graft failure. Applicants respectfully traverse the rejection of claims 5-8 and submit that the instant specification provides considerable guidance to the skilled artisan regarding how to overcome the hurdles previously documented in the prior art to achieve the claimed invention.

Applicants maintain their earlier position, as stated in the Reply to Examiner's Action filed July 12, 2001, that the majority of transplant studies using animal models clearly demonstrate the feasibility and success of transplanting embryonic and

nonembryonic RPE cells and that mitigating undesired immune reactions is not a significant barrier when dealing with transplanted RPE tissue in or near the retina. Furthermore, Applicants enclose herewith the Declaration of Dr. Vincent Tropepe, which presents data that clearly demonstrate that retinal stem cells and cells derived from retinal stem cells may be successfully transplanted into the eye using the methods of the instant invention and that transplantation occurs without adverse immune rejection (discussed below).

The Examiner states that:

> the skilled artisan would not accept on its face the proposition that retinal stem cells or cells differentiated from these cells could be transplanted without avoiding the significant hurdles explicitly taught by the cited references such that vastly different conditions recited in the present claims would be treated or ameliorated.

The Examiner argues that practicing the claimed invention would require undue experimentation. Applicants respectfully submit that a skilled artisan, once put in possession of the retinal stem cells of the present invention, would rely on the teachings in the specification and the general knowledge in the art with respect to transplantation of RPE cells into the eye (see, e.g., Muller-Jensen et al., Mod. Probl. Ophthamol. 15:228-234, 1975; Seigel et al., Cell Transplantation 7:559-566, 1998; provided herewith). The retinal stem cells, as taught in the specification, certainly were not known in the art and their existence was surprising and unexpected.

Applicants support their position by providing the enclosed Declaration of the co-inventor, Dr. Vincent Tropepe, which presents data that demonstrate the preparation of retinal stem cells for transplantation using the methods of the invention (see page 20, line 21, through page 23, line 11, of the specification), and the transplantation of the retinal

stem cells and their progeny into the eye using techniques known in the art (see e.g., Muller-Jensen et al., supra; Seigel et al., supra). As is indicated in the Declaration, the preparation and transplantation of retinal stem cells and their progeny is successful and devoid of an adverse immune reaction to the transplanted cells. The declaration demonstrates that retinal stem cells, isolated from donor mice carrying the green fluorescent protein (GFP) transgene, were cultured using techniques described in the instant specification on page 20, line 21, through page 23, line 11. Retinal stem cells and progeny (sphere cultures generated in culture) were dissociated and prepared as a cell suspension. The GFP-tagged cells were injected into the vitreous of the right eye of a newborn mouse of the same strain as the donor, but lacking the GFP transgene. Microscopic examination of the mice after 4 weeks indicated no gross histologic alterations in transplanted eyes compared to their uninjected counterparts. Green cells derived from retinal stem cells in culture were detected. These cells integrated normally into retinal tissue and were present in several layers of the multi-layered retina. The majority of the marked cells were not pigmented, even though all of the cells were descendants of pigmented retinal stem cells, showing that retinal progenitor cells integrated into the eye. Morphological and biochemical techniques (as taught on page 24, line 9, through page 25, line 10, of the instant specification) were used to verify that some of the transplanted GFP-tagged retinal stem cells differentiated into retinal neurons, in particular, photoreceptors. After 4 weeks, the vast majority of mice displayed normal ocular morphology with no evidence of immune rejection (i.e., there was no adverse immune response).

Applicants also enclose the text of an abstract presented on November 14, 2001 by another lab, Y. Kurimoti et al. (Soc. Neurosci. Abstr., vol. 31, Program No.791.11, 2001). The abstract shows that retinal stem cell transplants are successful and do not stimulate an adverse immune response. Furthermore, in an injured adult mouse eye model, retinal stem cells can differentiate into photoreceptors after transplantation into the subretinal space.

Based on the foregoing remarks, Applicants respectfully submit that they have clearly shown that transplantation of retinal stem cells and their progeny into the eye using the methods of the invention are successful and that there is no adverse immune reaction to the transplanted cells. Furthermore, one skilled in the art would be able to practice the invention of claims 5-8 using the guidance provided in the instant specification and the knowledge generally available in the field. Accordingly, Applicants respectfully request that the rejection of claims 5-8 be withdrawn.

## CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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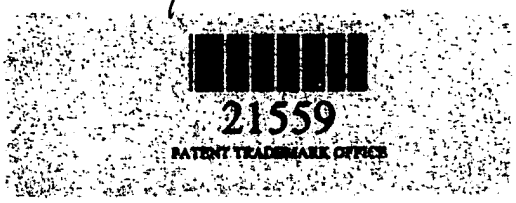


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